Autoinflammatory Disorders, Pain, and Neural Regulation of Inflammation

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KEYWORDS

• Autoinflammatory disorders • Neural crosstalk • IL-1β • Inflammasome • Pain • Neuromodulation

KEY POINTS

- Current dermatologic disorders with predominant inflammatory components, such as rosacea and acne, possess hallmark features of autoinflammatory disorders.
- The contribution of interleukin-1 beta (IL-1β) in mediating pain through underlying neural pathways is underappreciated in the context of autoinflammatory disorders, and needs to be further explored.
- Disorders marked by increases in IL-1β in the absence of adaptive immune activation, in conjunction with inexplicable pain and inflammation, may be considered diagnostic criteria for classifying autoinflammatory disorders.
- Further exploration into the causative link between inflammation and the nervous system may lead to new therapeutic modalities for autoinflammatory disorders, such as neuromodulation.

INTRODUCTION

Autoinflammatory disorders are a newly described class of disorders marked predominantly by dysregulation of the innate immune system.[1] This heterogeneous class of disorders is clinically distinct from autoimmune disorders.[1–3] Autoinflammatory disorders are currently recognized as "clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition."[1] Increased levels of interleukin-1 beta (IL-1β) cause abnormal inflammatory responses and are central to these disorders. Infection has yet to be found during episodic flares and does not seem to be a precipitating factor in the disorders. High-titer antibodies and antigen-specific autoreactive T cells are also absent.

A large number of disorders are now recognized as autoinflammatory and the number continues to grow. Affected systems are diverse and include skin, joints, and the nervous system.[1] The hereditary periodic fever (HPF) syndromes were among the first to be labeled as autoinflammatory.[2] Gout, type 2 diabetes, obesity-induced insulin resistance, Blau syndrome, and others are now classified as autoinflammatory.[1,4] Some autoinflammatory disorders, including pyogenic arthritis-pyoderma gangrenosum-acne (PAPA) syndrome and Blau syndrome, affect the skin.[5,6] Other dermatologic disorders with an inflammatory component, such as rosacea or acne, may potential be autoinflammatory disorders.

Many of the autoinflammatory disorders have a strong pain component that is overlooked. Episodic flares in the HPF syndromes and gout can cause debilitating pain. Cytokines, including

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IL-1β, and other inflammatory mediators are known to play important roles in neuronal perception of pain.[7] Thus abnormal innate immune responses may abnormally affect neuronal perception of pain. The nervous system plays an important role in regulating inflammation and inflammatory pain.[8] Neural-inflammation crosstalk may be disrupted in autoinflammatory disorders and contribute to the symptoms. Although crosstalk between inflammation and perception of pain is known to occur, it has not been highlighted in autoinflammatory disorders. Highlighting the inflammatory/neural crosstalk may allow a richer understanding of autoinflammatory disorders and potentially help to broaden the current disorder classification. This article provides an overview of current autoinflammatory disorders and how inexplicable inflammation and pain may factor into classifying new autoinflammatory disorders.

THE INFLAMMASOME

Identification of the inflammasome and its physiologic role helped to elucidate autoinflammatory disorders as being caused by dysregulation of the innate immune system. The inflammasome is a complex of proteins composed of a sensor protein, the adapter protein apoptosis-associated speck-like protein with CARD domain (ASC), and caspase-1.[9] Four sensor proteins have been identified: NLRP1, NLRP3, NLRC4, and AIM2.[10] Binding of stimuli to the sensor protein promotes assembly of the complex and activation of caspase-1. The NLRP1, NLRC4, and AIM2 inflammasomes are activated by specific microbial stimuli, whereas NLRP3 can be activated by a broad range of microbial and sterile stimuli.[4,9] Once activated, the inflammasome processes proIL-1β into its active form. IL-1β is a potent regulator of inflammatory responses. Activation of IL-1β in response to inflammatory stimuli is a 2-step process.[11] The first step involves increased production of proIL-1β. Basal expression of proIL-1β is low and is induced by nuclear factor (NF)-κB.[11] Activation of NF-κB occurs through pathogen-associated molecular patterns (PAMPs) that stimulate phagocytic cells or through primary cytokines.[12] The second step is activation of inflammasomes.

The NLRP3 inflammasome is the most studied inflammasome. Microbial activation can occur through bacteria, fungi, and viruses.[13–15] Unlike other inflammasomes, the NLRP3 inflammasome can be activated in sterile environments by nonmicrobial stimuli; extracellular ATP, monosodium crystals, calcium pyrophosphate dehydrate crystals, cholesterol crystals, and oligomers of islet amyloid polypeptide are all capable of activating NLRP3 inflammasomes.[16–19] Several of these nonmicrobial activators are also involved in the pathogenesis of other diseases with a strong inflammatory component such as gout and type 2 diabetes. Thus a broad range of stimuli or genetic defects can cause dysregulation of the innate immune system and induce an autoinflammatory response. In the established HPF syndromes and the emerging autoinflammatory disorders, dysregulation of the innate immune system, specifically the inflammasome, is at the epicenter and abnormal inflammasome activity results in increased IL-1β levels.

INFLAMMASOME AUTOACTIVATION DISORDERS

Familial Mediterranean fever (FMF) is an HPF disorder. Patients with FMF experience episodic bouts of fever and serosal inflammation lasting up to 3 days and occurring every 10 days to once a year.[20] During attacks, patients also experience debilitating muscle and joint pain.[21] Defects in the *MEFV* gene encoding for pyrin have been found to cause FMF.[22] Pyrin is a regulator of capsase-1 activation. The defective pyrin protein causes an overactive inflammasome, which leads to increased levels of IL-1β.[23]

Mutations in the *PSTPIP1* (proline-serine-threonine-phosphatase interacting protein 1) gene have been identified as the cause of PAPA syndrome.[24] PAPA syndrome is an autosomal dominant hereditary syndrome that has some clinical similarities to FMF. Sterile arthritis of the knees, elbows, and ankles develops in early childhood in patients with PAPA.[25] Symptoms also include cystic acne and pyoderma gangrenosum, which last into adulthood and may cause debilitating pain.[5] Infection has yet to be found in cultures from skin lesions or joint fluids.[5,24] PSTPIP1 interacts with pyrin to regulate inflammasome activity.[26] Mutations result in hyperphosphorylation of PSTPIP1 disrupting regulation of the NLRP3 inflammasome, which causes increased production of IL-1β.

The cryopyrin-associated periodic syndromes (CAPSs) are a group of 3 syndromes that are also HPF syndromes: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). FCAS is the least severe and is characterized by cold-induced fever and rashes.[11] MWS is more severe and is accompanied by hearing loss and arthritis. NOMID is the most severe and is characterized by chronic fever, hives, hearing loss, overgrowth of the epiphyses of the long bones, chronic meningitis, cerebral atrophy, and delayed atrophy.[27] All 3 are caused by

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